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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,338	12/09/2004	Sven Ole Warnaar	2923-672	2944

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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,338	WARNAAR ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-10 and 12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claims 1-17 are pending, claims 6, 7, and 11 are withdrawn from consideration as being drawn to a non-elected invention, and claims 1-5, 8-10, and 12-17 are under consideration.

2. Applicant's election with traverse of Group II in the reply filed on August 18, 2006 is acknowledged and has been entered. The traversal is on the grounds that the groups of inventions are properly linked by a special technical feature because the reference that was cited as disclosing the special technical feature, Mulders (2002, Curr. Urol. Rep. 3(1):44-9) only discloses the combination for therapy of a monoclonal antibody and cytokines in the abstract and in the last paragraph of conclusions and that this disclosure is speculative. This argument is not found persuasive because the disclosure constitutes an anticipation of the special technical feature for restriction purposes. The requirement is proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-5, 8, 10, 12-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4, 5, 8, 10, 12-17 are objected to because the phrases "low-dose form" and "low-dose cytokine" are relative terms which render the claim indefinite. The term "low-dose form" and "low dose cytokine" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Although the specification specifies on page 5 that "the administration of

"low-dose cytokine" according to the present invention means that the cytokine is administered in a dose which is pharmaceutically effective in improving the efficacy of an antibody therapy in the substantial absence of toxic side effects, e.g. in the substantial absence of NIC CTC toxicity grade 3 or higher" the definition itself is indefinite in that the term "substantial " is indefinite and in that the dose at which NIC CTC toxicity grade 3 or higher develops is likely to vary from patient to patient. Amendment of the claims to clarify exactly what is intended by the claims is required.

Claim 14 is objected to because of the recitation of the phrase "chimeric G250 antibody". The exact meaning of the word chimeric is not known. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. Amendment of the claim to clarify exactly what is intended by the claim is required.

Claims 3 and 10 are objected because of the recitation of the phrases "substantial" and "substantially", respectively. The words "substantial" and "substantially" are 'indefinite terms and one of skill in the art would not be able to ascertain the metes and bounds of the claims.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 1-5, 8-10, and 12-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of a cancer comprising co-administering an anti-tumor antibody directed against the MN

antigen and a cytokine to a subject in need thereof, wherein the cytokine is administered continuously or repeatedly in a low-dose form, wherein the cancer is renal cell carcinoma, does not reasonably provide enablement for a method for the treatment of a cancer comprising co-administering an anti-tumor antibody and a cytokine to a subject in need thereof, wherein the cytokine is administered continuously or repeatedly in a low-dose form, wherein the cancer is any cancer .

The claims, as drawn to the elected invention, are as follows:

a method for the treatment of a cancer comprising co-administering an anti-tumor antibody and a cytokine to a subject in need thereof, wherein the cytokine is administered continuously or repeatedly in a low-dose form (claim 1),

wherein the low-dose cytokine comprises a dose which is pharmaceutically effective in the substantial absence of NIC CTC toxicity grade 3 or higher (claim 3),

comprising a daily administration of a low-dose cytokine (claim 4),

wherein the cytokine is an interferon (claim 5),

wherein the cytokine is an interferon, wherein the cytokine is IFN-α (claim 8),

wherein the cytokine is an interferon, wherein the cytokine is IFN-α, wherein the dose of IFN-α is in the range of from 1-10 MIU three times a week (claim 9),

wherein the cytokine is administered in a substantially constant dose during the treatment. (claim 10),

wherein the cytokine is administered subcutaneously (claim 12),

wherein the antitumor antibody is selected from antibodies directed against the MN (G250) antigen (claim 13),

wherein the antitumor antibody is a chimeric or humanized G250 antibody or a fragment thereof (claim 14),

wherein the antitumor antibody is administered in intervals of from 5-20 days. (claim 15),

wherein the first treatment stage comprises 5-20 days (claim 16),

wherein the second treatment stage comprises 50-200 days (claim 17),

and

a method for the treatment of a cancer comprising co-administering an anti-tumor antibody and cytokine to a subject in need thereof, wherein the method comprises: (a) a first treatment stage comprising administering a low-dose cytokine, and (b) a second treatment stage comprising co-administering an anti-tumor antibody and a low-dose cytokine (claim 2),

wherein the first treatment stage comprises 5-20 days (claim 16),

wherein the second treatment stage comprises 50-200 days (claim 17).

The specification teaches a clinical trial comprising coadministering of chimeric G250 antiibody and IFN in patients with advanced renal cell cancer, wherein patients received a subcutaneous injection of IFN-α (3 MIU per dose) three times a week on days 1, 3 and 5 of the first week, a weekly infusion of cG250 on day 1 during weeks 2-12 with the same IFN-α schedule as above, and the same treatment during weeks 17-22 as for weeks 2-12 for all patients approved for extension of treatment (Example 2). The specification also teaches that the combination treatment of cG250 and IFN- α was well tolerated, with no serious adverse effects related to cG250 observed and only moderate adverse events typical for IFN-α observed (Example 2). The specification also teaches that preliminary results show the presence of a clinical benefit for the treated patient group (Example 2).

The teaching of the specification cannot be extrapolated to enable the scope of the claims because one of skill in the art could not predict that the invention would function as claimed in treating any cancer. In particular, different cancers have different etiology and characteristics, and expression or overexpression of a protein in a specific cancer is not necessarily the same as that for the same protein in another type of cancer. For example, Busken, C et al, Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850, teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). The specification teaches that an antibody to the MN antibody, the G250 antibody, is effective in treating cancer in combination with low dose *IFN-α* in patients with advanced renal cell cancer, but does not teach that antigen is expressed or over expressed in other types cancer or that the G250 antibody is effective in inhibiting an y other type of cancer. Further, Vissers et al. (1999, Cancer Research 59:5554-5559) teaches that the antigen G250 is renal cell carcinoma associated antigen that is expressed on 85% of RCCs and that can be detected on the cell surface of colon, ovarian and cervical carcinomas. Thus based on the teaching in the art and in the specification, one of skill in the art could not predict that the MN antigen is overexpressed or expressed in cancers other than renal cell carcinoma to the extent required for the claimed methods of treating cancer. Thus, undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1, 3, 4, 10, 12, 13, and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Beck et al., (March 2002, Proceedings of the American Association for Cancer Research, as described in the specification on page 3) as evidenced by Uemura (1999, Brittish J. of Cancer 81(4):741-746).

The claims are as follows:

a method for the treatment of a cancer comprising co-administering an anti-tumor antibody directed against the MN antigen and a cytokine to a subject in need thereof, wherein the cytokine is administered continuously or repeatedly in a low-dose form (claim 1),

wherein the low-dose cytokine comprises a dose which is pharmaceutically effective in the substantial absence of NIC CTC toxicity grade 3 or higher (claim 3),

comprising a daily administration of a low-dose cytokine (claim 4),

wherein the cytokine is administered in a substantially constant dose during the treatment. (claim 10),

wherein the cytokine is administered subcutaneously (claim 12),

wherein the antitumor antibody is selected from antibodies directed against the MN (G250) antigen (claim 13),

wherein the antitumor antibody is administered in intervals of from 5-20 days. (claim 15),

Beck et al. teaches a phase I/II trial with the monoclonal antibody G250 in combination with low dose IL-2 in metastatic RCC, wherein patients received G250

once weekly via intravenous infusion and IL-2 subcutaneously according to an alternating low dose and periodic pulsing treatment scheme over 6 weeks (1.8 MIU or 5.4 MIU IL-2 per day, single dose). Beck et al. also teaches that the treatment was well tolerated and showed a therapeutic response.

As evidenced Uemura, the monoclonal antibody G250, raised against a human renal cell carcinoma (RCC) has been shown to react with a large number of RCCs and tthe G250 antigen has been found to be homologous with the MN/CA9 antigen (abstract).

Thus, all of the claim limitations are met.

Although Beck et al. does not specifically teach the absence of NIC CTC toxicity grade 3 or higher, given the teaching in Beck et al. that the treatment was well tolerated, it would be expected that the toxicity of the treatment was below the specified level. Thus, the claimed method appears to be the same as the prior art method. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the prior art does not possess the same method steps of the claimed process. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed methods of treating cancer are different than those taught by the prior art and to establish patentable differences. See In re Best 562 F.2d 1252, 195 USPQ430 (CCPA 1977) and Ex Parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 2, 5, 8, 9, 14, 16 and 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al., (March 2002, Proceedings of the American Association for Cancer Research, as described in the specification on page 3), and further in view of Bleumer et al., (January 2002, European Urology Supplements, Vol. 1, No. 1, pp. 112) and Pavone (2001, Cancer Immunol. Immunother. 50:82-86).

The claims, as drawn to the elected invention, are as follows:

a method for the treatment of a cancer comprising co-administering an anti-tumor antibody directed against the MN antigen and a cytokine to a subject in need thereof,

wherein the cytokine is administered continuously or repeatedly in a low-dose form wherein the cytokine is an interferon (claim 5),

wherein the cytokine is IFN-α (claim 8),

wherein the cytokine is IFN-α, wherein the dose of IFN-α is in the range of from 1-10 MIU three times a week (claim 9),

wherein the antitumor antibody is a chimeric or humanized G250 antibody or a fragment thereof (claim 14),

and

a method for the treatment of a cancer comprising co-administering an anti-tumor antibody directed against the MN antigen and cytokine to a subject in need thereof, wherein the method comprises: (a) a first treatment stage comprising administering a low-dose cytokine, and (b) a second treatment stage comprising co-administering an anti-tumor antibody and a low-dose cytokine (claim 2),

wherein the first treatment stage comprises 5-20 days (claim 16),

wherein the second treatment stage comprises 50-200 days (claim 17).

Beck et al. teaches as set forth above but does not teach the administration of a chimeric G250 antibody, or a first treatment stage that comprises a low dose cytokine and second treatment stage that comprises an antibody and a cytokine, or that the cytokine is IFN-α .

Bleumer et al. teaches a phase II clinical trial with monoclonal antibody WX-G250, a chimeric monoclonal antibody, in patients with advanced renal cell carcinoma, wherein the patients were pretreated (e.g. with IL-2 and interferon-alpha) and weekly dose of WX-G250 was given by iv infusion for 12 weeks. Bleumer et al. concluded tha

the weekly schedule of WX-G250 was safe, and very well tolerated for the 12 week treatment regimen.

Pavone et al. teaches that there is no standard treatment for advanced renal cell carcinoma (RCC), but that recombinant interleukin-2 (rIL-2) and interferon-α (rIFN-a) have produced good results to inducing objective responses and especially prolonged survival, although the optimal dose and schedule of immunotherapy have yet to be determined (page 82). Pavone further teaches a study wherein patients having advanced renal cell carcinoma were treated with a combination therapy of rIL-2, given by subcutaneous injection for 5 days per week ($1x10^6$ IU/m^2 every 12 h on days 1 and 2, followed by $1x10^6$ IU/m^2 on days 3-5), and rIFN-a given twice a week (1.8 x 106 IU/m2 on days 3 and 5) for four consecutive weeks, with the cycle being systemically repeated every 4 months) (page 83). Pavone et al. further teaches that the above described study indicated that long-term repeated cycles of low doses of rIL-2 and rIFN-a were found to induce a repeated and significant expansion of CD3-CD56+ NK cells, one of the most important lymphocyte subsets for the immune response to tumoral antigens, with the results supporting the long-term repetitive treatment of tumors susceptible to immunotherapy (page 86).

It is prima facie obvious to combine the G250 antibody treatment with cytokine continuous treatment taught by Beck with the G250 antibody treatment with cytokine pretreatment taught by Bleumer to arrive at a method wherein the cytokine is administered both before antibody treatment and coincident with antibody treatment for the treatment of renal cell carcinoma. Further, it would have obvious to combine either of the treatments with the low dose cytokine combination taught by Pavone. The idea of combining them flows logically from their having been individually taught in prior art (e.g. In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been

individually taught in the prior art). One of skill in the art would have been motivated to combine the therapies because of the known intractability of renal cell carcinoma to therapy. One of skill in the art would have a reasonable expectation of success in making the combination because of the demonstrated success of each to therapeutic methods individually. Further, as set forth in MPEP 2144.05, in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. In re Wertheim 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).
Further, it would have prima facie obvious for one of skill in the art to have titrated the administration protocols for the combination of the anti-tumor antibody directed against the MN antigen and low dose cytokines in order to optimize the efficacy of the combined anti-renal cell carcinoma therapy to arrive at first treatment stage of 5-20 days and given the convention nature of such titration.

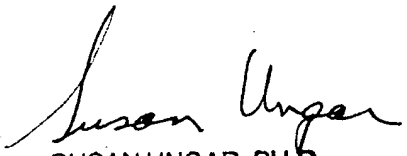
11. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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